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Time in therapeutic range and major adverse outcomes in atrial fibrillation patients undergoing percutaneous coronary intervention: the AFCAS Registry

Marco Proietti MD, K.E. Juhani Airaksinen MD, Andrea Rubboli MD, Axel Schlitt MD, Tuomas Kiviniemi MD, Pasi P. Karjalainen MD, Gregory YH Lip MD

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Time in therapeutic range and major adverse outcomes in atrial fibrillation patients undergoing percutaneous coronary intervention: the AFCAS Registry

Marco Proietti[1] MD, K.E. Juhani Airaksinen[2] MD, Andrea Rubboli[3] MD, Axel Schlitt[4] MD, Tuomas Kiviniemi[5] MD, Pasi P. Karjalainen[6] MD, Gregory YH Lip[1,7] MD on behalf of the AFCAS Study Group

[1]Institute of Cardiovascular Sciences, University of Birmingham, Birmingham, United Kingdom; [2]Heart Center, Turku University Hospital and University of Turku, Turku, Finland; [3]Division of Cardiology, Laboratory of Interventional Cardiology, Ospedale Maggiore, Bologna, Italy; [4]Department of Medicine III, Martin Luther-University, Halle, Germany; [5]Department of Cardiology, Paracelsus Harz-Clinic, Bad Suderode, Germany; [6]Heart Center, Satakunta Central Hospital, Pori, Finland; [7]Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark.

Short Title: TTR in AF with PCI-S

Corresponding Author:

Prof. GYH Lip

University of Birmingham Institute of Cardiovascular Sciences, City Hospital

Dudley Road, B18 7QH, Birmingham, United Kingdom

Tel: +44 121 5075080; Fax: +44 121 5544083; g.y.h.lip@bham.ac.uk

ABSTRACT

Background: Combination of oral anticoagulation (OAC) and antiplatelets is used in atrial fibrillation (AF) patients undergoing percutaneous coronary intervention and stent (PCI-S) procedure, but is associated with increased bleeding when triple antithrombotic therapy (TAT) is used. Our aim was to analyse the impact of time in therapeutic range (TTR) on outcomes, in patients prescribed with TAT.

Methods: Ancillary analysis from the AFCAS registry in patients assigned to TAT. TTR was calculated with Rosendaal method. Outcomes were analysed according to TTR tertiles (T1[≤56.8%]vs.T2[56.9-93.8%]vs.T3[≥93.9%]). Major bleeding was the primary outcome.

Results: Of 963 patients enrolled, 470(48.8%) were prescribed with TAT at discharge and qualified for this analysis. Median [IQR] TTR was 80.0%[45.3-100%]. After 359[341-370] days, major bleeding rates were progressively lower with increasing TTR tertiles (T1vs.T2vs.T3:10.3%vs.4.7%vs.2.3%,p=0.006).

Kaplan-Meier analysis demonstrated a progressively lower risk for major bleeding across tertiles (p=0.006). Patients in the highest TTR tertile had a non-significant lower risk for major adverse coronary and cerebrovascular events (MACCE)(Log-Rank: 4.905, p=0.086).

Cox regression analysis showed that T2 and T3 were inversely associated with major bleeding (hazard ratio[HR]:0.39,p=0.050 and HR:0.21,p=0.005). Continuous TTR was inversely associated with major bleeding (HR:0.98,p<0.001). For MACCE, adjusted Cox analysis found a non-significant lower risk for T3 (HR:0.64,p=0.128).

Conclusions: In AF patients undergoing PCI-S prescribed TAT, good quality anticoagulation control (as reflected by TTR) was closely related to bleeding outcomes during follow-up. Despite some suggestive trends for an inverse relationship between TTR and MACCE, no definitive conclusions can be drawn, and further large studies are needed.

Keywords: atrial fibrillation; percutaneous coronary intervention; triple antithrombotic therapy; anticoagulation control; outcomes.

INTRODUCTION

In patients with atrial fibrillation (AF), concomitant coronary artery disease is often present (1). Many uncertainties still exist about the concomitant use of antiplatelet and oral anticoagulation (OAC) therapy in this clinical setting, especially in AF patients undergoing percutaneous coronary intervention with stenting (PCI-S) (2). Indeed, a balance should be obtained between stroke prevention in AF (which requires OAC), stent thrombosis and recurrent cardiac ischemia (both requiring dual antiplatelet therapy) and serious bleeding (by combining OAC with antiplatelet therapy).

The use of triple antithrombotic therapy (TAT), namely aspirin, any P2Y12 inhibitor (*i.e.* clopidogrel, prasugrel, ticagrelor) and OAC with a vitamin K antagonist (VKA), is associated with a higher risk for serious bleeding (3), despite targeting lower international normalized ratio (INR) values (3). An increased risk of bleeding with TAT has been documented, in hospitalized AF patients(4) and in those following myocardial infarction (MI) or a PCI-S (5).

Major guidelines (6,7) currently recommend initial TAT, even if only for a short period of time, followed by a period of single antiplatelet therapy plus OAC up to 12 months after PCI-S. In 2014, the joint European consensus document endorsed by the Heart Rhythm Society and Asia-Pacific Heart Rhythm Society on the management of AF patients presenting with an acute coronary syndrome or undergoing PCI-S was published, which recommended evaluation of thromboembolic (CHA_2DS_2-VASc score) and bleeding (HAS-BLED score) risks, followed by consideration of antithrombotic strategy based on presentation (acute vs. elective) and type of stent (8). However, thromboembolic and bleeding risks with VKA are closely related to quality of anticoagulation control, as reflected by time in therapeutic range (TTR) within an INR 2.0-3.0(9).

The Atrial Fibrillation Undergoing Coronary Artery Stenting (AFCAS) registry was a prospective multicentre European registry including AF patients undergoing PCI-S. Baseline and 1 year outcomes from AFCAS have been previously published (10,11). The objective of this ancillary study from AFCAS was to relate major adverse outcomes, primarily major bleeding, in AF patients prescribed TAT after a PCI-S to quality of anticoagulation control, as reflected by TTR. Secondary outcomes were cardiovascular/cerebrovascular events.

METHODS

The AFCAS registry was an observational, prospective, multicentre study about the clinical management of AF patients undergoing PCI-S. In brief, all AF patients referred for a PCI-S procedure were eligible to take part in the study. A 12-months follow-up observation period was planned in order to record all major adverse outcomes. For this study, all patients prescribed TAT at discharge after the PCI-S procedure with complete data about clinical characteristics, follow-up observation and available data about TTR throughout the study follow-up period were analysed.

Thromboembolic risk was categorised according to CHA_2DS_2-VASc score(12). "Low risk" patients were defined as males with a CHA_2DS_2-VASc =0 or females with CHA_2DS_2-VASc =1; "moderate risk" was defined as male patients with CHA_2DS_2-VASc=1; and "high risk" with CHA_2DS_2-VASc ≥2. TTR was calculated according to Rosendaal interpolation method(13). INRs considered for TTR calculation were performed at baseline and at every subsequent follow-up visits (1 month, 3 months, 6 months, 12 months). Baseline INR range was 2.0-3.0 in 456 out of 470 patients (97.0%), while 6 patients were in the lower range (INR<2.0) and 8 patients were in the higher range (INR>3.0). Effective anticoagulation control using VKA was defined as a TTR >70%(14).

To fulfil the aims of this study we performed two distinct analysis: first, we evaluated the "dose-effect" response between progressively higher TTR tertiles and the occurrence of outcomes. Second, we evaluated the effect of having best quality anticoagulation control (*i.e.* the highest TTR tertile, compared to others) in relation to major adverse events. Last, we tested the relationship between effective anticoagulation control (*i.e.* TTR >70%) and major adverse events in a sensitivity analysis.

Based on the original protocol, the principal safety outcomes were 'major bleeding', defined as intracranial, bleeding requiring blood transfusion or surgical/endoscopic treatment or leading to long-term disability or death, and 'clinically relevant non-major bleeding' (CRNMB), which was bleeding requiring no treatment or leading to ambulatory management with no surgical/endoscopic treatment.

Furthermore, the principal efficacy outcome was a composite of major acute cardiovascular/cerebrovascular events (MACCE), including acute MI, target vessel revascularization, stroke/transient ischemic attack (TIA), systemic embolic event, stent thrombosis and cardiovascular death. Acute MI was defined according to the universal definition in use at the time of the study (15). Target vessel revascularization was defined as PCI-S or coronary bypass surgery in the previously treated vessel. Stent thrombosis was defined according to the Academic Research Consortium classification and included definite and probable events(16). TIA was defined as a focal, transient (<24 hours) neurological deficit adjudicated by a neurologist, whereas stroke was defined as a permanent, focal, neurological deficit adjudicated by a neurologist and confirmed by computed tomography/magnetic resonance imaging. Systemic embolism was defined as

signs/symptoms of peripheral ischemia associated or not with a positive imaging test. Cardiovascular death was defined as a death related to cardiac cause or stroke.

Statistical Analysis

Patients were categorized according to TTR tertiles, defined as follows: 1st Tertile (T1) <56.8%; 2nd Tertile (T2) 56.9-93.8%; 3rd Tertile (T3) >93.9%. Continuous variables were reported as median [IQR] and differences between subgroups were assessed with Kruskal-Wallis 1-way ANOVA test. Categorical variables, expressed as counts and percentages, were analysed by chi-squared test, with Bonferroni correction for evaluation of pairwise comparisons between groups.

Differences in survival were analysed using the log-rank test and Kaplan-Meier analysis according to TTR tertiles and, additionally, comparing patients in T3 to those in the other two tertiles combined. In order to establish if TTR was independently associated with major bleeding and MACCE a Cox proportional-hazards analysis, adjusted for age, gender, AF type, CHA_2DS_2-VASc score, PCI-S clinical indication and PCI-S clinical setting for both outcomes, was performed. Two distinct models were performed using TTR tertiles, both comparing T1, T2 and T3 distinctly, and secondly, comparing T3 to the other two tertiles. Furthermore, we constructed a third model using TTR as a continuous variable. A two-sided p value <0.05 was considered statistically significant. In the additional sensitivity analysis, a similar analytical approach was followed using the log-rank test and Kaplan-Meier analysis for TTR >70%, followed by Cox proportional-hazards analysis using the same adjustments. All analyses were performed using SPSS v. 22.0 (IBM, NY, USA).

RESULTS

Of the 963 patients originally enrolled in the AFCAS study, 470 (48.8%) patients were eligible for this ancillary analysis. These patients subdivided according to TTR tertiles were as follows: 145 (30.8%) in T1; 149 (31.7%) in T2; 176 (37.4%) in T3. As expected, median TTR values across tertiles progressively increased [Figure 1].

Baseline characteristics according to TTR tertiles are shown in Table 1. Patients in the three TTR tertiles did not show significant differences in the baseline characteristics except for the prevalence of diabetes mellitus, higher in T1 compared to T2 and T3 (p=0.034). Previous gastrointestinal bleeding was more prevalent in T2 patients (p=0.030). Femoral vascular access was progressively less prevalent from patients in T1 to T3 (p=0.006).

Follow-Up and Survival Analysis

After a median [IQR] follow-up of 359 [341-370] days, a total of 26 (5.5%) major bleeding and 58 (12.3%) CRNMB events occurred, whilst 82 (17.4%) MACCE were recorded. At 12-months follow-up, 52 (11.1%) patients were still on triple therapy; no significant differences were found between the three tertiles (data not shown).

Outcomes according to TTR tertiles are shown in Table 2. Major bleeding rate progressively decreased from T1 to T3 patients (p=0.006). For MACCE, patients in T2 reported the highest event rate (21.5%), while patients in T3 reported the lowest rate of MACCE (11.9%); this difference was not statistically significant (p=0.066).

Survival analysis found a progressive decrease in cumulative risk for major bleeding across the three TTR tertiles (Log-Rank: 10.320, p=0.006) [Figure 2, Left Panel]. A non-significant trend for progressively lower MACCE risk was found [Figure 2 Right Panel] (Log-Rank: 4.905, p=0.086).

Comparing patients in the highest TTR tertile (T3) to those in the other two (T1-T2), a lower risk for major bleeding was confirmed in T3 [Figure S1, Left Panel; Log-Rank: 5.770, p=0.016). A lower risk for MACCE was found in T3 compared to T1-T2 (Log-Rank: 4.420, p=0.036) [Figure S1, Right Panel].

A multivariable Cox regression analysis (Table 3) showed that both T2 and T3 tertiles were inversely associated with major bleeding (p=0.050 and p=0.005, respectively). Model 2 confirmed that the best anticoagulation control (T3) had the lowest risk for major bleeding (p=0.027). The third Cox model, with TTR as a continuous variable, showed that TTR was inversely associated with major bleeding (p<0.001).

For MACCE, the Model 1 adjusted Cox analysis found a non-significant lower risk for patients in T3 (p=0.128). In Model 2, obtaining the best anticoagulation control was inversely associated with MACCE events occurrence (T3 vs. T1/T2, p=0.033). The final model with continuous TTR showed a non-significant trend for an inverse relationship with MACCE (p=0.069).

Sensitivity Analysis

We performed a sensitivity analysis taking the TTR >70% cut-off as reference (Supplementary Materials). Major bleeding was significantly lower in patients with TTR >70% compared to those with TTR ≤70% (2.2% vs. 10.0%, respectively; p<0.001). There was a non-significant trend for lower MACCE events (14.1% vs. 20.5%, respectively; p=0.065) (Table S1). Kaplan-Meier curves

[Figures S2-S3] confirmed a significantly lower risk for major bleeding with TTR >70% [Figure S2]. Cox regression analysis (Table S2) found that TTR >70% was independently associated with a lower risk for major bleeding ($p<0.001$).

DISCUSSION

In our study of AF patients undergoing a PCI-S procedure prescribed with TAT, our principal finding is that good anticoagulation control in VKA users, as reflected by a high TTR, was inversely associated with both major bleeding and MACCE. Specifically, we show a progressive stepwise risk reduction for major bleeding when going from lowest to higher TTR tertiles. Similarly, patients with the best anticoagulation control had the lowest risk of major bleeding compared to all the other patients. As far as we are aware, we provide the first data relating major bleeding to TTR in the setting of PCI-S and AF.

Several studies have shown that AF patients prescribed TAT have a higher risk for major bleeding. In a large cohort derived from the Danish nationwide cohort study, patients on TAT had almost four-fold higher risk for the composite of major fatal and non-fatal bleeding (hazard ratio [HR]: 3.70, 95% confidence interval [CI]: 2.89-4.76), with no reduction in stroke occurrence (HR: 1.45, 95% CI: 0.84-2.52)(4). More recently, a the Get-With-The-Guidelines programme reported an increased risk for bleeding-related hospitalizations for AF patients prescribed TAT, with a 2-fold increased risk of intracranial haemorrhage-related hospitalizations (HR: 2.04, 95% CI: 1.25-3.34)(17). No difference was found in efficacy outcomes when comparing TAT patients with those prescribed dual antiplatelet therapy (17).

Other registry evidence has confirmed a higher risk of bleeding associated with TAT, with up to a 2-fold higher risk for any bleeding (HR: 2.08, 95% CI: 1.64-2.65), with a higher short-term risk, as well as a significant association with fatal bleeding at 30 days after discharge (HR: 1.85, 95% CI: 1.27-2.70)(5); however, there was also a significant reduction in ischemic stroke (HR: 0.67, 95% CI: 0.46-0.98), all-cause death (HR: 0.61, 95% CI: 0.47-0.77) and the composite outcomes for AF

patients treated with TAT(5). Similar data have been reported in elderly patients, with a 5-fold increased risk for major bleeding, with concomitant reductions of thromboembolic events and all-cause death (18). However, all these registry studies do not provide data in relation to TTR.
In this context, our data show how the risk of bleeding during TAT is dependent on the quality of anticoagulation control, as reflected by the TTR.

Despite being inconclusive for MACCE, our data are suggestive of the importance of the quality of anticoagulation control in obtaining improved outcomes(19–21). Our three tertiles were mostly comparable in clinical characteristics, additional residual confounders could have influenced the increased rate of MACCE for patients in T2, beyond the quality of anticoagulation control. Nevertheless, patients in T3 had the lowest rate of MACCE events suggesting that better control of TTR may lower the risk. Larger prospective studies would be needed to confirm these trends.

Several published studies have reported how TTR is a strong predictor of both thromboembolic-related and bleeding-related outcomes, independent from body weight(22), renal function(23) and gender(24). Moreover, the importance of anticoagulation control in properly evaluating potential bleeding risk has been recently shown (25,26). In a large systematic review, Wan et al clearly show an inverse linear association between TTR and outcomes, both bleeding and thromboembolic (9). More recently, a large observational study confirmed the inverse relationship between TTR and adverse outcomes(27).

The joint European consensus document recommends evaluation of the balance between thromboembolic and bleeding risks, then minimizing the period of TAT treatment to 4 weeks in patients with a high risk of bleeding (HAS-BLED ≥3), followed by 12 months of single antiplatelet

therapy with clopidogrel and OAC, either with a VKA (e.g. warfarin) or non-vitamin K antagonist oral anticoagulant (NOAC)(8). For VKA therapy, a narrower therapeutic range is recommended (INR 2.0-2.5) and for NOACs, the lower approved dose for stroke prevention in AF should be used (8). In the WOEST trial, clopidogrel plus warfarin was associated with a reduced risk of any bleeding (Iargely driven by reduction in minor bleeds) compared to TAT without any increase in thrombotic events (28). Despite that, WOEST did not provide any data in relation to TTR. Our results substantiate the recommendations in the European consensus document on maintaining optimal anticoagulation control while taking VKA.

Recently, results from the "Open-Label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects with Atrial Fibrillation who Undergo Percutaneous Coronary Intervention" (PIONEER AF-PCI)(29) showed that the two arms with different rivaroxaban doses, 15 mg and 2.5 mg, resulted in a significantly lower risk of any significant bleeding (TIMI major or TIMI minor bleeding or bleeding requiring medical attention) compared to VKA therapy (HR: 0.59, 95% CI: 0.47-0.76 and HR: 0.63, 95% CI: 0.50-0.80 respectively for rivaroxaban 15 mg and rivaroxaban 2.5)(30). Despite a significant reduction of recurrent hospitalization (particularly those related to bleeding and cardiovascular reasons)(31), this study did not show significant reduction in all major adverse cardiovascular events, due to limited power(30). The overall TTR recorded for the VKA arm was 65%, but the use of NOACs in this setting seems encouraging. Several ongoing randomised clinical trials would provide additional evidence (32).

Limitations

The main limitation of this study is the post-hoc subgroup retrospective design, which was not powered to detect differences in the specified subgroups, warranting further confirmation from adequately powered prospective studies. Even if the groups considered were comparable according to the baseline characteristics, the presence of additional confounders cannot be completely excluded and fully accounted for. Also, the limited number of patients still on TAT at 1 year follow-up would represents another limitation. Nonetheless, we still show important associations particularly for bleeding events, in relation to tertiles of TTR. Some suggestive trends for an inverse relationship between TTR and MACCE, but our data do not allow us to draw definite conclusions, requiring further adequately powered studies to confirm this aspect.

In conclusion, in AF patients undergoing a PCI-S prescribed TAT, good quality anticoagulation control (as reflected by TTR) was closely related to better bleeding outcomes during follow-up. Despite some suggestive trends for an inverse relationship between TTR and MACCE, no definitive conclusions can be drawn, and further large studies are needed.

AUTHORS' CONTRIBUTION

MP and **GHYL** conceived the study, analysed data, interpreted results and drafted the manuscript. **KEJA**, **AR**, **AS**, **TK**, **PPK** coordinated the original study, collected data and provided critical evaluation of the manuscript. **MP** and **GYHL** takes full responsibility for manuscript content. All authors read and approved the manuscript.

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DISCLOSURES OF INTEREST

MP: Consultant for Boehringer Ingelheim; **TK**: Consultant for Boehringer Ingelheim. Speaker for Bayer, BMS/Pfizer, Boehringer Ingelheim; **GYHL**: Consultant for Bayer/Janssen, BMS/Pfizer, Biotronik, Medtronic, Boehringer Ingelheim, Microlife and Daiichi-Sankyo. Speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Microlife, Roche and Daiichi-Sankyo. No fees are received personally.

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FIGURES LEGENDS

Figure 1: TTR values distribution according to tertiles.

Legend: TTR= time in therapeutic range. Dashed line and error bars= Median [IQR].

Figure 2: Kaplan-Meier curves for major adverse events according to TTR tertiles.

Legend: MACCE= major adverse cardiac/cerebrovascular events.

Table 1: Baseline characteristics according to TTR tertiles

	1st Tertile n= 145	**2nd Tertile** n= 149	**3rd Tertile** n= 176	**p**
Age, (years) median [IQR]	74 [68-78]	74 [69-79]	74 [29-79]	0.760
Female, n (%)	42 (29.0)	42 (28.2)	49 (27.8)	0.975
BMI, (kg/m2) median [IQR]	28 [25-32]	28 [25-31]	28 [25-30]	0.606
CrCl, (ml/min) median [IQR] *403*	69.6 [54.1-94.4]	68.0 [50.3-89.1]	71.9 [57.4-94.8]	0.333
TTR, (%) median [IQR]	28.1 [4.1-42.7]	76.0 [63.5-83.4]	100.0 [98.8-100..0]	<0.001
Prescribed TAT Duration, n (%)				0.687
0-3 months	68 (46.9)	79 (53.0)	90 (51.1)	
3-6 months	36 (24.8)	29 (19.5)	43 (24.4)	
≥6 months	41 (28.3)	41 (27.5)	43 (24.4)	
AF Type, n (%) *464*				0.951
Paroxysmal	42 (29.2)	43 (29.7)	46 (26.1)	
Persistent	15 (10.4)	13 (9.0)	18 (10.2)	
Permanent	87 (60.4)	89 (61.4)	111 (63.4)	
Hypertension, n (%)	115 (79.3)	121 (81.2)	142 (80.7)	0.914
Hypercholesterolemia, n (%)	95 (65.5)	106 (71.1)	112 (63.6)	0.341
Diabetes Mellitus, n (%)	59 (40.7)	44 (29.5)	49 (27.8)	0.034
Smoking Habit, n (%)	13 (9.0)	10 (6.7)	15 (8.5)	0.750
Coronary Artery Disease, n (%)	47 (32.4)	49 (32.9)	69 (39.2)	0.353
Previous MI, n (%)	36 (24.8)	35 (23.5)	45 (25.6)	0.909
Previous PCI, n (%)	18 (12.4)	17 (11.4)	28 (15.9)	0.453
Previous CABG, n (%)	25 (17.2)	32 (21.5)	23 (13.1)	0.132
Chronic Heart Failure, n (%)	27 (18.6)	28 (18.8)	23 (13.1)	0.282
Ejection Fraction, (%) median [IQR]	50 [40-60]	52 [40-60]	50 [40-60]	0.968
Previous Stroke/TIA, n (%)	28 (19.3)	27 (18.1)	36 (20.5)	0.869

Previous Bleeding, n (%)	2 (1.4)	10 (6.7)	6 (3.4)	0.055
Previous Cerebral Bleeding, n (%)	1 (0.7)	2 (1.3)	2 (1.1)	0.856
Previous GI Bleeding, n (%)	1 (0.7)	7 (4.7)	2 (1.1)	0.030
Previous GU Bleeding, n (%)	0 (0.0)	1 (0.7)	1 (0.6)	0.632
CHA_2DS_2-VASc, median [IQR]	3 [3-5]	3[3-5]	4 [2-4]	0.718
Thromboembolic Risk, n (%)				0.331
Low Risk	0 (0.0)	2 (1.3)	3 (1.7)	
Moderate Risk	8 (5.5)	15 (10.1)	15 (8.5)	
High Risk	137 (94.5)	132 (88.6)	158 (89.8)	
PCI Clinical Indication, n (%)				0.903
Stable Angina	61 (42.1)	70 (47.0)	80 (45.5)	
NSTE-ACS	59 (40.7)	54 (36.2)	66 (37.5)	
STEMI	19 (13.1)	20 (13.4)	20 (11.4)	
Other	6 (4.1)	5 (3.4)	10(5.7)	
PCI Clinical Setting, n (%)				0.449
Emergency	70 (48.3)	73(49.0)	96 (54.5)	
Urgency	56 (38.6)	53 (35.6)	64 (36.4)	
Elective	19 (13.1)	23 (15.4)	16 (9.1)	
N° Diseased Vessels, median [IQR]	2 [1-3]	2 [1-3]	2 [1-3]	0.460
N° Treated Vessels, median [IQR]	1 [1-1]	1 [1-1]	1 [1-1]	0.717
Lesion Type, n (%) *444*				0.398
A	24 (18.2)	21 (15.3)	22 (12.6)	
B1/B2	83 (62.9)	81 (59.1)	118 (67.4)	
C	25 (18.9)	35 (25.5)	35 (20.0)	
Vascular Access, n (%)				0.006
Radial	36 (24.8)	53 (35.6)	77 (43.8)	
Femoral	107 (73.8)	96 (64.4)	98 (55.7)	
Other	2 (1.4)	0	1 (0.6)	

Complete Revascularization, n (%) *463*	65 (46.8)	65 (43.6)	86 (49.1)	0.611
Stent Type, n (%) *464*				0.361
DES	36 (25.0)	38 (25.9)	41 (23.7)	
Bioactive	25 (17.4)	37 (25.2)	37 (21.4)	
BMS	78 (54.2)	66 (44.9)	82(47.4)	
Other	5 (3.5)	6 (4.1)	13 (7.5)	

Legend: ACS= acute coronary syndrome; AF= atrial fibrillation; BMS= bare metal stent; CABG= coronary artery by-pass graft; DES= drug eluting stent; GI= gastro-intestinal; GU= genital-urinary; IQR= interquartile range; MI= myocardial infarction; NSTE= non ST elevation; PCI= percutaneous coronary intervention; STEMI= ST elevation myocardial infarction; TIA= transient ischemic attack.

Table 2: Major adverse events at follow-up according to TTR tertiles

	1st Tertile	2nd Tertile	3rd Tertile	p
	n= 145	n= 149	n= 176	
Major Bleeding, n (%)	15 (10.3)	7 (4.7)	4 (2.3)	0.006
CRNMB, n (%)	21 (14.5)	19 (12.8)	18 (10.2)	0.505
MACCE, n (%)	26 (17.9)	32 (21.5)	21 (11.9)	0.066

Legend: CRNMB= clinical relevant non-major bleeding; MACCE= major adverse cardiac/cerebrovascular events; MI= myocardial infarction; TIA= transient ischemic attack.

Table 3: Cox regression analysis for major adverse events*

	Hazard Ratio	95% CI	p
Major Bleeding			
Model 1			
TTR 1st Tertile	Ref.	Ref.	Ref.
TTR 2nd Tertile	0.39	0.15-1.00	0.050
TTR 3rd Tertile	0.21	0.07-0.63	0.005
Model 2			
TTR 1st/2nd Tertiles	Ref.	Ref.	Ref.
TTR 3rd Tertile	0.30	0.10-0.87	0.027
Model 3			
TTR (%)	0.98	0.97-0.99	<0.001
MACCE			
Model 1			
TTR 1st Tertile	Ref.	Ref.	Ref.
TTR 2nd Tertile	1.21	0.72-2.04	0.474
TTR 3rd Tertile	0.64	0.36-1.14	0.128
Model 2			
TTR 1st/2nd Tertiles	Ref.	Ref.	Ref.
TTR 3rd Tertile	0.58	0.35-0.96	0.033
Model 3			
TTR (%)	0.99	0.99-1.00	0.069

Legend: *adjusted for age, gender, AF type, CHA_2DS_2-VASc, PCI-S clinical indication, PCI-S clinical setting. AF= atrial fibrillation; MACCE= major adverse cardiac/cerebrovascular events; PCI= percutaneous coronary intervention; TTR= time in therapeutic range.

Figure 1

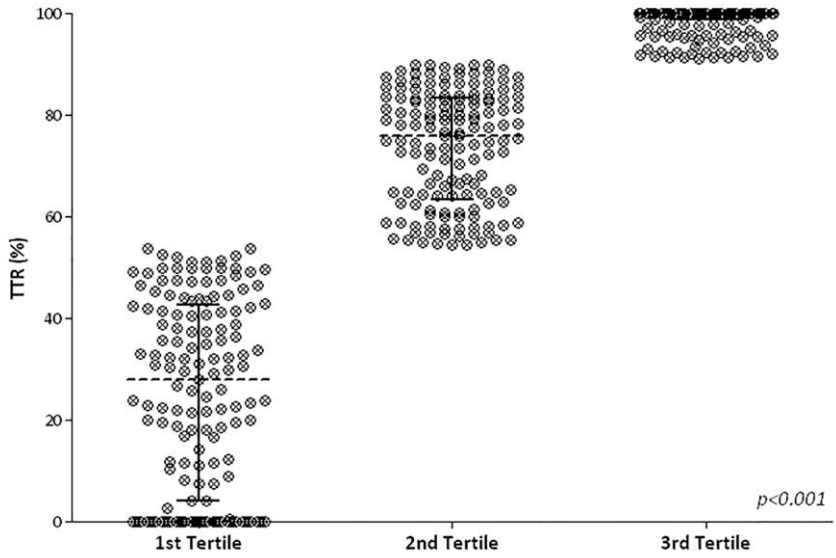
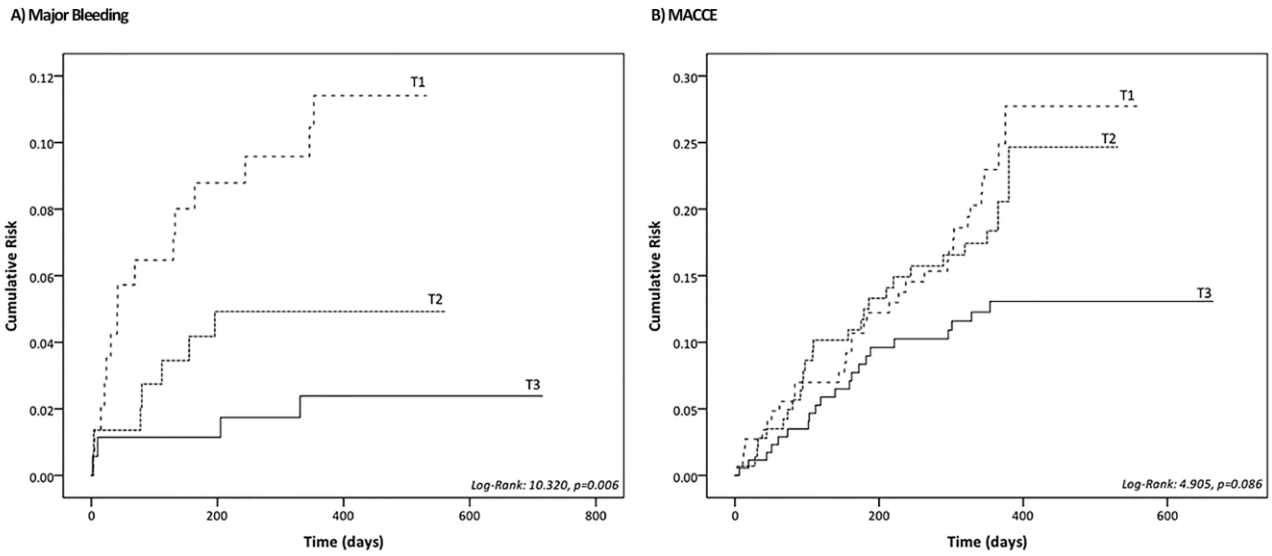


Figure 2



HIGHLIGHTS

- Atrial fibrillation (AF) is associated with significant coronary artery disease
- In AF patients undergoing stenting, triple antithrombotic therapy (TAT) is often used
- Use of TAT in AF patients is associated with a higher risk of bleeding
- Time in therapeutic range (TTR) is associated with better bleeding outcomes
- High TTR during TAT in AF after stenting is associated to improved bleeding outcomes